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KRSEK STAPLES, T
EXAMINER

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 7-10-95 Amdt B & 10-10-95 Amdt C ☑ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-7, 10 + 22-33 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 8, 9 + 11-21 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-7, 10 + 22-33 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Applicant's amendment filed July 10, 1995 and supplemental amendment filed October 10, 1995 has been entered. Claims 11-21 have been cancelled and claims 32 and 33 have been added and claims 1-7 and 10-33 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1802.

Rejections and Objections which are Withdrawn

The objection to the disclosure because of informalities is withdrawn.

The objection to the specification regarding the description of the graph on page 24 is withdrawn.

The rejection of claims 1-7, 10 and 22-31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment of the claims.

The rejection of claims 22, 26, and 27 under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the amendment of the claims.

The rejection of claims 1-6 and 22-29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,290,551 is withdrawn in view of the amendment of the claims.

All previous rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103 have been withdrawn in view of the amendment of the claims.

The following objection to the specification and the rejection of claims 1, 4-7, 10 and 22, 23 and 25-31 under 35 U.S.C. § 112, first paragraph based on this objection is withdrawn because claims 1 and 22 have been amended as a method for and composition for treating melanoma:

> The specification specifically teaches a melanoma vaccine and describes immune responses to the melanoma vaccine and clinical results (p 19-43). While the specification states that cancers treatable with the present invention include those listed above, the specification does not teach how to select tumor cells or extracts which would be effective in treating these other cancers.

The following objection to the specification and the rejection of claims 1-7, 10 and 22-31 under 35 U.S.C. § 112, first paragraph based on this objection is withdrawn because the claims have been amended to recite a conjugated hapten:

> As stated above, the specification discloses that all vaccines were DNP-conjugated and that the control group of patients received non-haptenized autologous melanoma vaccine (p 29). Therefore, the specification specifically teaches non-haptenated cells and an adjuvant, as recited in the composition claim, do not prevent against melanoma. The specification also does not provide guidance for the addition of a hapten to the composition which is not chemically linked to the tumor cell. Because haptens are only immunogenic when bound to a carrier, one of skill in the art would not expect that the addition of free hapten to tumor cells or tumor cell extracts would induce the same type of immune response as the DNP-conjugated compositions disclosed in the specification.

Rejections which are Maintained

Because the tumor cell extracts have been amended in the claims as comprising a peptide, portions of the rejection regarding tumor cell extracts which include cell-surface associated proteins, proteins encoded by cancer oncogenes or mutated oncogenes or chemicals unique or substantially specific to a particular type of cancer has been deleted. The rejection set forth in the previous Office Action is maintained as follows:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The claimed invention is directed to a method and a pharmaceutical composition for treating cancer including melanoma, lung cancer, colon cancer, breast cancer, kidney cancer and prostate cancer. The specification specifically teaches a melanoma vaccine and describes immune responses to the melanoma vaccine and clinical results (p 19-43). While the specification states that cancers treatable with the present invention include those listed above, the specification does not teach how to select tumor cells or extracts which would be effective in treating these other cancers.

The specification states that extracts of the present invention comprise a peptide isolated from cancerous cells (p 12). The specification discloses that cancer specific extracts include peptides binding to the major histocompatibility complex (p 12). The specification cites Rotzschke et al as teaching the isolation of peptides form cells and states that the fractions obtained by this method are screened for immunological activity by allowing them to bind to autologous B lymphoblastoid cells which are then tested for ability to stimulate melanoma-specific T lymphocytes (paragraph bridging pages 16-17).

The specification does not characterize such extracts comprising isolated peptides. The method of Rotzschke et al describes the isolation of viral peptides from major histocompatibility complex class I molecules in tumor cells infected with virus. The peptides isolated in this procedure are not specifically tumor-derived peptides but rather are viral peptides. Therefore, the specification does not provide guidance for the isolation and identification of tumor cell extracts as defined above. The specification also does not provide guidance for treating the other cancers listed above using tumor cells or tumor cell extracts comprising isolated peptides.

The treatment of cancer using tumor antigens is unpredictable as discussed by Bystryn. Bystryn teaches that tumor antigens selected for therapy must a) be able to induce clinically effective immune responses in humans; b) be expressed on the tumor to be treated; c) be located at a site on the tumor where they can interact with immune effector mechanisms (p 83, paragraph bridging columns 1 and 2). Bystryn also teaches that other variables such as the tumor load of the patient may also play a role in the effectiveness of the tumor antigen for therapy (p 85, column 1).

The specification does not provide guidance for selecting specific tumor antigens which meet this criteria and would be expected to function as a therapeutic agent against cancers other than melanoma when administered in the claimed vaccine composition. The use of autologous melanoma cells for the treatment of melanoma cannot be extrapolated to the use of tumor cells and tumor cell extracts to treat other forms of cancer. Bystryn teaches that for cancer immunotherapy to be effective the immune responses induced must be directed to antigens being expressed by the tumor being treated. Bystryn discloses the pattern of tumor antigens expressed by cancers of the same histological type in different individuals is variable. Bystryn also teaches that there is variation in the pattern of tumor antigens expressed by different tumor cells of the same histological type in the same individual (p 84 paragraph 1). Furthermore, the profile of tumor antigens expressed by a tumor during its progression may be altered by the immune

response of the host as a result of antigenic modulation. Bystryn also discloses that as a consequence of this variability it is unlikely that vaccines prepared from a single tumor antigen will be effective against a broad range of tumors of the same histological type and for the same reason autologous vaccines may not be effective against other tumor cells in the same patient (p 84, column 1).

In a review article by Finn, several potential tumor antigens are discussed and Finn states that the likelihood of finding antigens on tumors that will truly be tumor-rejection antigens is great. But as of 1993, these antigens had not yet been identified as Finn summarized in the conclusion of the paper:

> The term 'tumor-rejection antigens' used in the title of this review does not accurately reflect the nature of the molecules discussed. In fact every author whose work was reviewed has carefully avoided using this term, because very few molecules identified so far can be implicated in tumor rejection. The term is used here to primarily support the notion that many such molecules exist....The research community recognizes that having a tumor-specific antigen or peptide does not guarantee that anti-tumor responses will be generated *in vivo*, or that these responses will prevent or inhibit tumor growth. Given the diversity of the molecules reported this year, and the potential diversity of those that will be found in the near future, the likelihood of finding antigens on tumors that will truly be tumor-rejection antigens is great".

The melanoma vaccine disclosed in the specification consists of irradiated autologous melanoma cells. The specification does not teach that the administration of melanoma vaccine or other cancer vaccine using allogeneic tumor cells would be effective in treating cancer. Hellstrom et al disclose that allogeneic tumor cells or extracts used as immunogens may not induce cytotoxic lymphocyte (CTL) response because there may be a lack of major histocompatibility complex (MHC) matching between the immunogen and the patient's lymphocytes (p 29, paragraph 7). For the reasons discussed above, a vaccine composition for the treatment of one type of cancer cannot be extrapolated to other types of cancer and the effectiveness of either allogenic or autologous tumor antigens in treating cancer also unpredictable.

The sentence bridging pages 27-28 in the specification states that "All vaccines were DNP-conjugated and mixed with Bacille Calmette-Guerin" (BCG). The method claims have recently been amended to exclude the recitation of an adjuvant. However, it appears that including BCG may be a critical method step. Livingstone et al disclosed that in a melanoma vaccine using the GM2 ganglioside, antibody responses were not induced unless BCG was added to the purified GM2 vaccine (p 2913, paragraph bridging columns 1 and 2). Livingstone et al also state that "Adjuvants and pretreatment with low doses of cyclophosphamide were important

factors in the mouse studies, and results of the present human trials indicate their importance in melanoma patients" (p 2914, column 1). Hoover et al also used BCG as an adjuvant in a colorectal cancer vaccine and states that the correct amount of the appropriate adjuvant (i.e. BCG) was a critical condition of the success of the immunotherapy (p 1242, column 1, paragraph 2). The specification also does not provide guidance for using a pharmaceutical composition in which the melanoma cells are not irradiated. It would be expected that irradiation would be necessary to prevent the cells from growing following injection. Based on the teachings above, one of skill in the art would not expect that the claimed method would be effective in treating melanoma without specifically including BCG as demonstrated in the specification and one of skill in the art would not expect that the claimed composition would be effective without using irradiated tumor cells.

Claims 1-7, 10 and 22-31 and newly added claims 32-33 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

New Grounds of Rejection

Claims 1-7, 10, and 22-33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 22, 32 and 33 the term "tumor cell extracts comprising a peptide" is vague. The specification states that "Extracts of the present invention comprise a peptide isolated from cancerous cells" (see page 12). However, this definition is not clear because tumor cell extracts are not equivalent to an isolated peptide. While tumor cell extracts may contain proteins, they do not contain isolated peptides because once a peptide is isolated, it is no longer a part of the tumor cell extract. Therefore, it is not clear whether these claims comprise the administration of a tumor cell extract or a peptide isolated from a tumor cell. It is also not clear from the

phrase "irradiated composition" which portion of the composition is irradiated. For example, it is not clear whether the tumor cells from which the extracts are derived are irradiated or whether the isolated peptide is irradiated.

It is noted on page 5 of Applicant's remarks that, by definition recognized by those of skill in the art, peptide includes the definition of a protein as peptides and proteins include more than one amino acid linked by the carboxyl group of one amino acid to the amino group of another amino acid. This statement would imply that the amended claims are intended to include both peptides and proteins. While both peptides and proteins consist of amino acids linked by peptide bonds, peptides are not the same as proteins. *Harper's Biochemistry* textbook gives the following definitions of peptides and proteins: A peptide consists of 2 or more amino acid residues linked by peptide binds. Peptides of more than 10 amino acid residues are termed polypeptides. All proteins are high-molecular-weight polypeptides. (see pages 24 and 32, first paragraphs). The specification also states that peptides will preferably be a low molecular weight, about 9 to about 20 amino acids (p 12). While the above claims are vague in terms of whether the tumor cell extracts or isolated peptides are administered or included in the composition, contrary to Applicant's remarks, the term "peptide" is not read to be the same as "protein" in view of the art-recognized definitions above.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The claimed invention is directed to a method and a pharmaceutical composition for treating either melanoma or other cancers including lung cancer, colon cancer, breast cancer, kidney cancer and prostate cancer by the administration of a composition comprising an irradiated composition of tumor cell extracts comprising a peptide. The specification specifically teaches the administration of autologous irradiated melanoma cells conjugated to DNP and mixed with BCG and describes immune responses to the melanoma vaccine and clinical results (p 19-43). The specification does not teach the administration of an irradiated composition of tumor cell extracts comprising a peptide conjugated to a hapten or a mixture of tumor cells and the above peptide. For the detailed reasons set forth in the previous rejection under 35 U.S.C. § 112, first paragraph and again presented above, it is maintained that it would require undue experimentation to determine which peptides to administer for the treatment of melanoma and other cancers. In addition, the specification does not teach how to make and use tumor cell extracts comprising a peptide for a tumor such as lung, colon , breast, kidney or prostate in the treatment of melanoma. Because of the variability in tumors as discussed above, one of skill in the art would not expect that a peptide isolated from a kidney tumor, for example, would be effective in treating melanoma. Due to the unpredictability in identifying tumor rejection antigens

as discussed above, it would require undue experimentation to determine which peptides from one type of tumor could be used to treat another type of cancer.

Claims 1-7, 10 and 22-31 and newly added claims 32-33 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Response to Applicants' Arguments

In the response submitted July 10, 1995, Applicant argues that while the method of Rotzschke et al of isolating peptide has been adapted, the present invention is not directed to viral infection. Applicant argues that the other reference used in support of the rejection under 35 U.S.C. § 112, first paragraph, are taken out of context. Applicant argues that the references cited above do not provide the required for burden for a showing of enablement. Applicant argues that the burden of proof required to establish enablement and written description has been met and the burden has now shifted to the Examiner.

Applicants' arguments have been considered but are not deemed to be persuasive. It is maintained that the specification does not teach how to make and use the invention for the reasons cited in the rejections above. The references used in support of the rejection are not taken out of context and specifically address the unpredictability of identifying an using tumor antigens in the treatment of various cancers, problems with using allogenic tumor cell extracts, and the criticality of the use of an adjuvant all of which are relevant to the claimed invention.

In the response filed October 10, 1995, Applicant states that the data in the specification is sufficient to demonstrate patentable utility and compliance with the requirements of 35 U.S.C. § 112, first paragraph. Applicants state that those having ordinary skill in the art would accept Applicant's data presented therein as sufficient to establish that Applicant has taught how to make and use the invention and that the claimed method would be *prima facie* believable to those having ordinary skill in the art. Applicants further argue issues relating to the utility of the rejection. Applicants cite *In re Brana* in support that the requirements under the law for obtaining a patent are not to be confused with the requirements for obtaining government approval to market a particular drug for human use. Applicant's statement that "The present invention is not directed to the treatment of cancer" is confusing because claim 32 specification recites "A method for treating cancer". In addition, there is clearly a misplaced paragraph on page 7 of the response which refers to an invention and a declaration by an inventor which is not the current invention or inventor.

Applicant's arguments have been considered but are not deemed to be persuasive. Applicant's cite *In re Brana* in support that the requirements under the law for obtaining a patent are not to be confused with the requirements for obtaining government approval to market a particular drug for human use. However, the issues in *In re Brana* are not the same as that of the above rejection. In *In re Brana* the main issue was whether the *in vivo* animal models were sufficient to demonstrate whether the claimed antitumor compounds in *In re Brana*, which were structurally similar to compounds known in art, had antitumor properties. The issue in the instant Application does not involve an animal model because human clinical data has been

presented. The issue in the instant Application involves the unpredictability of using the claimed compositions and methods in context of the broad scope of the claims in view of what is known in the art about tumor antigens and cancer treatments. It is noted that a utility rejection has not been made against the pending claims and that the reasons why the specification does not teach how to make and use the claimed compositions of tumor cell extracts comprising a peptide as been set forth above. As discussed above, all of the data presented in the specification involved the treatment of melanoma while the claims are broadly drawn to treating may different cancers, and using tumor cell extracts from several different cancers to treat melanoma. In addition, the composition and method presented in the data of the specification are not the same as the claimed methods and compositions. The data in the specification demonstrates the use of autologous irradiated tumor cells rather than tumor cell extracts comprising peptides and the methods of the specification include an adjuvant. Because the data in the specification is not commensurate with the scope of the claims and due to the unpredictability of the various aspects of the invention as discussed in the rejection above, it is maintained that the specification does not teach how to make and use the invention as claimed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie K. Staples whose telephone number is (703) 305-7556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission via the PTO Fax Center, located in Crystal Mall 1. The Fax Center number is (703) 305-7939. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

JKS
Julie K. Staples, Ph.D.
December 15, 1995

James C. Housel
JAMES C. HOUSEL 12/19/95
SUPERVISORY PATENT EXAMINER
GROUP 180